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Screening of a Supramolecular Catalyst Library in the Search for Selective Catalysts for the Asymmetric Hydrogenation of a Difficult Enamide Substrate**

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Transition-metal-catalyzed asymmetric hydrogenation is one of the classic success stories in transition-metal catalysis because it has resulted in several scientific breakthroughs[1] as well as the development of commercial processes.[2] Many highly enantioselective catalysts for the asymmetric hydrogenation of various classes of prochiral substrates have been reported.[3] However, there are still many challenging substrates that cannot be converted with satisfactory enantioselectivities or yields, which has led to the ongoing intensive research efforts in this area. Although computational techniques are becoming increasingly important, one cannot design an enantioselective chiral catalyst in silico, and therefore, catalyst development for asymmetric reactions relies to a

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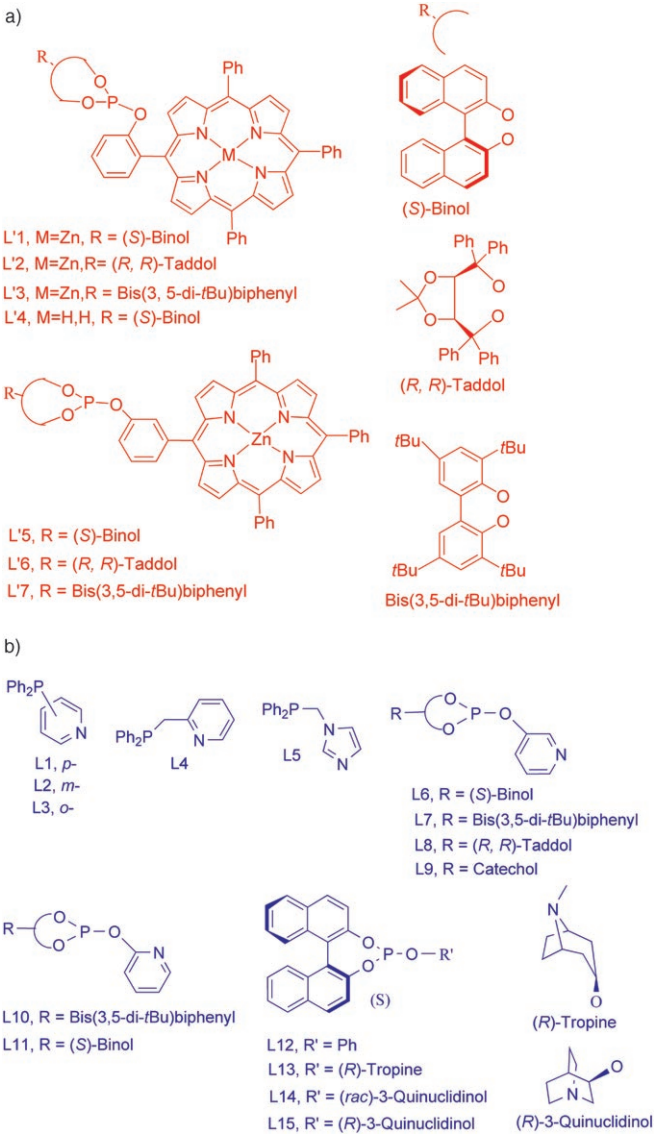
great extent upon a trial-and-error approach and sophisticated guesses. Consequently, combinatorial approaches and high-throughput experimentation have become increasingly important.[4] Several elegant screening techniques for combinatorial catalysis have been developed, but there is only limited technology available to prepare large catalyst libraries with sufficient diversity. Interesting breakthroughs include the revival of the use of monodentate ligands,[5] simultaneously reported by the research groups of Reetz,[6] Feringa and de Vries,[7] and Pringle,[8] and more recently, the successful use of mixtures of monodentate ligands.[9,10] Lefort et al. accomplished the robotic synthesis of 96 monodentate phosphoramidites (instant ligand libraries) and robotic screening in asymmetric hydrogenation in just two days, which demonstrates the value of simple ligand structures.[11] Although some interesting modular bidentate ligands have been reported,[12] a similar breakthrough and revival in the field of bidentate-ligated transition-metal catalysts[13] would be of great impetus for asymmetric catalysis. Consequently, we,[14] and others,[15] have recently introduced a new class of bidentate ligands resulting from the self-assembly of two monodentate ligands (Figure 1). We have used the zinc(II)porphyrin–pyridyl interaction as an assembly motif to generate bidentate phosphorus-based ligands. We have also shown that only 14 building blocks were required to generate a library of 48 bidentate phosphorus ligands,[14b] which have been used successfully in hydroformylation[14a,c] and asymmetric allylic alkylation reactions.[14b,c] Herein we report the extension of the supraphos library and its application in the asymmetric rhodium-catalyzed hydrogenation of a trisubstituted cyclic enamide, which yielded unprecedented selectivities.

The supraphos ligand consists of two components (displayed in red and blue in Figure 1) brought together by the selective and reversible coordination of the nitrogen donor atom of ligand L to the zinc atom of L′, and both phosphorus ligands can then simultaneously coordinate to the rhodium metal (green). For the current study we have used 7 porphyrin–phosphites, including newly prepared zinc(II)porphyrins functionalized with taddol phosphite (L′2 and L′6), and 14 phosphorus ligands containing pyridyl (and other N-donor) groups (Scheme 1). The building blocks were obtained



Scheme 1. a) Structures of porphyrin-functionalized phosphites. b) Structures of N-containing phosphorus ligands.

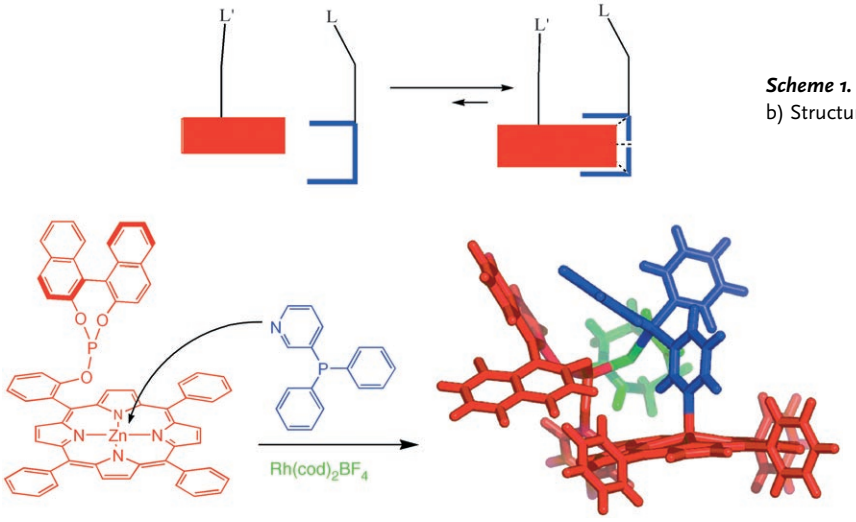
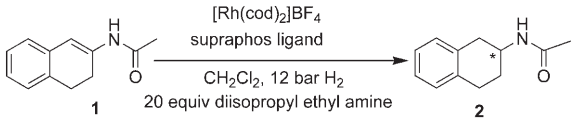


Figure 1. The formation of a bidentate ligand and its transition-metal complex by self-assembly.

by simple synthetic routes (see the Supporting Information), and the supraphos ligand library was constructed with these building blocks according to Figure 1. This library was used in the rhodium-catalyzed hydrogenation of one of the most challenging benchmark substrates in asymmetric hydrogenation, *N*-(3,4-dihydro-2-naphthalenyl)-acetamide (**1**; Scheme 2), by using high-throughput methods to perform 96 reactions in parallel (0.04 mmol scale).[11,16] There are only a few ruthenium-based catalysts known to produce product **2** with high enantioselectivities (up to 90%) from this commercially interesting sub-



Scheme 2. Rh-catalyzed hydrogenation of *N*-(3,4-dihydro-2-naphthalenyl)acetamide (**1**).

strate.[17] Rhodium catalysts generally result in low to moderate *ee* values (< 72 %) for the product.[18]

The results of the screening experiments displayed in Table 1 show that the supraphos-based catalysts induced conversions from 0 to 100 % and *ee* values between −12 and 94 %. The best results, in terms of conversion and *ee* values, are highlighted in red, and it is clear that there is no correlation between the *ee* value and the conversion. The catalyst based upon supraphos ligand L′1/L2 provides the highest *ee* value (94 %) reported to date and full conversion. Results from five other members of the library indicate that greater than 90 % conversion was obtained, but the highest *ee* value was only 56 %, which represents a significant decrease from 94 %.

In general, both phosphine-phosphite ligands and bisphosphites can provide catalysts that lead to high conversions and *ee* values up to 56 %. Supraphos ligands based on binol-based porphyrin phosphites (L′1, L′5) induced, with a few exceptions, much higher conversions and selectivities than the taddol-based porphyrin phosphites (L′2, L′6). A small variation in ligand structure results in a large change in catalyst performance, as is often observed in asymmetric catalysis. For example, the structural differences between *o*-, *m*-, and *p*-pyridyl-substituted phosphines (L1, L2, and L3) seems small, but in combination with L′1 they result in the formation of rhodium catalysts with substantially different conversions and *ee* values of the product. The same is true when a simple CH_2 group bridges the pyridyl group and phosphorus (L4) or when a methylimidazol group is used instead of pyridyl (L5).

As the performance of L′1/L2 was exceptional we studied this supraphos ligand in more detail. ^{31}P NMR spectroscopy of a 1:1:1 mixture of [Rh(cod)$_2$]BF_4, L′1, and L2 in CD_2Cl_2 showed exclusive formation of the expected [Rh(L′1)(cod)(L2)]BF_4 complex (cod = cycloocta-1,5-diene; see the Supporting Information). The performance of supraphos ligand L′1/L2 as well as some important control experiments were studied on a larger scale (1 mmol of the substrate), and the conversion was monitored by H_2 uptake (Table 2). As expected, the results from the screening experiments were reproduced on this scale (Table 2, entry 1). Similar *ee* values were obtained, and the product was completely characterized after isolation by column chromatography and crystallization.

Several experiments indicate that the bidentate character of the supraphos ligand system is important. In contrast to the catalyst based on supraphos ligand L′1/L2, those based on L′4/L2 (an identical structure but without the zinc metal crucial for bidentate ligand assembly) and L′1/PPh_3, generated the product with only 10 % and 24 % *ee*, and at low conversions (Table 2, entries 2 and 3). The catalysts based on monodentate ligands such as [Rh(L12)$_2$] (Table 2, entry 5) and [Rh(L′1)$_2$] (20 % *ee*) also provided low selectivities and high conversions.

We studied the performance of the catalyst based on supraphos ligand L′1/L2 under various conditions. The reaction carried out with 1 mol % catalyst resulted in formation of the product with a high *ee* value (Table 2, entry 6). The metal-to-ligand ratio as well as the ratio of L′1/L2 is of importance for optimal catalyst performance. At high ligand loading, the *ee* value is high, but the activity is much lower (Rh/L′1/L2 = 1:1.5:1.5; Table 2, entry 7). Interestingly, the presence of only a small excess of L′1 does not affect the results (Rh/L′1/L2 = 1:2:1; Table 2, entry 9), thus indicating that under these conditions catalysis is dominated by the supraphos bidentate ligand. [Rh(L′1)$_2$] is more active and less

Table 1: Conversions (%) of **1** and *ee* values of **2** induced by the rhodium catalysts based on various supraphos ligands as obtained from screening experiments.[a–c]

	L1	L2	L4	L5	L6	L7	L8	L9	L10	L11	L13	L14
L′1	44	100	62	5	80	40	36	20	31	97	86	65
L′2	5	10	2	1	8	4	7	0	9	11	21	14
L′5	38	88	29	28	67	18	19	8	9	100	84	96
L′6	48	54	70	15	59	14	83	8	9	73	93	90

Conversion

	L1	L2	L4	L5	L6	L7	L8	L9	L10	L11	L13	L14
L′1	27	94	47	20	13	54	49	17	11	-2	56	13
L′2	5	7	8	5	16	-3	6	0	3	-12	16	10
L′5	24	46	18	14	21	52	31	11	21	30	34	28
L′6	-1	26	-4	0	5	-7	-12	6	5	4	-9	-5

ee value

100-90 90-80 80-70 70-60 60-50 50-40 40-30 30-20 20-10 10-0

[a] Reaction condition: [Rh(cod)$_2$]BF_4, Rh/L′*n*/L*n* = 1/1.5/1.2, 5 mol % rhodium, CH_2Cl_2, 12 bar H_2, 40 °C, 0.04 mmol of substrate **1**, 20 equiv diisopropyl ethyl amine, 14 h. [b] Conversion and *ee* were determined by chiral GC (Chiralsil-DEXCB). Negative *ee* values indicate that the opposite enantiomer was the major product. [c] Supraphos ligands based on achiral porphyrin-phosphite L′3, L′7 (in combination with chiral building blocks L6, L8, L11, L13, L15) gave *ee* values below 18 %, supraphos ligand L′1/L15 gave only slightly higher *ee* values (17 % *ee*, full conversion) than L′1/L14; for details see the Supporting Information.

Table 2: Different combinations and ratios of L′*n*/L*n* as catalysts.[a]

Entry	Ligand system	Rh/L′*n*/L*n*	Time [h][b]	Conv. [%][c]	*ee* [%][c]
1	L′1/L2	1/1.5/1.2	4	100	94 (+)
2	L′1/PPh_3	1/1.5/1.2	4	56	24 (+)
3	L′4/L2	1/1.5/1.2	14	19	10 (+)
4	L′1/L3	1/1.5/1.2	4	20	17 (+)
5	L12	1/0/2.1	4	85	1 (−)
6[d]	L′1/L2	1/1.5/1.2	14	86	93 (+)
7	L′1/L2	1/1.5/1.5	14	100	92 (+)
8	L′1/L2	1/1.5/1	14	100	92 (+)
9	L′1/L2	1/2/1	14	100	93 (+)
10	L′1/L2	1/1.2/1	14	100	64 (+)
11	L′1/L2	1/0.5/0.5	14	100	9 (+)
12	binaphos[e]	–	14	100	60 (+)

[a] Reaction conditions: 1 mmol of substrate **1**, 5 mol% $[Rh(cod)_2]BF_4$, CH_2Cl_2, 12 bar H_2, 25 °C, 20 equiv diisopropyl ethyl amine. [b] The time required for the reaction to go to completion based on H_2 uptake and GC analysis. [c] Conversion and *ee* were determined by chiral GC (Chiralsil-DEXCB). The optical signs in brackets are referenced to literature data.[17a] [d] 1 mol% catalyst. [e] 1.1 equiv with respect to Rh.

selective than the Rh/L′1/L2 system so it cannot be a dominant species during this experiment. Using low ligand/rhodium ratios results in faster reactions and lower selectivities, which indicates that other active rhodium species are formed under these conditions (Table 2, entries 10 and 11).

In view of the superior results of supraphos ligand L′1/L2, we considered it likely that the phosphine-phosphite combination plays a crucial role. Therefore we studied binaphos,[19] a covalent bidentate phosphine–phosphite ligand that has been applied successfully to many asymmetric transformations,[20] but in this case the enantioselectivity was moderate (60%, Table 2, entry 12). Chemical modification of binaphos might also lead to better selectivities, but this is a much more tedious process than modification of the supraphos ligand. To date, there is no covalent bidentate ligand that equals the best result obtained with a supraphos-based catalyst, which suggests that the supraphos ligand displays new ligand properties. The large aromatic surface of the porphyrin may play an important role because it creates a pocket to accommodate the substrate. In addition, the supraphos strategy facilitates the formation of ligand combinations that may not form, at least in significant quantities, by only using mixtures of monodentate ligands.[9,10]

In summary, we have demonstrated that the supraphos concept provides easy access to large bidentate ligand libraries and that these ligands can successfully be applied in rhodium-catalyzed asymmetric hydrogenation. High-throughput screening of the current library revealed a catalyst that hydrogenates the trisubstituted cyclic enamide **1** with the highest enantioselectivity known to date. This unambiguously shows that a supramolecular approach to create bidentate ligands is a very powerful tool which leads to new catalysts with properties that surpass those currently available. From the library of 64 supraphos ligands investigated, only one provides a catalyst that induced high *ee* values, which stresses the point that large ligand libraries are required for challenging asymmetric conversions, such as the hydrogenation of the trisubstituted cyclic enamide **1**. One of the advantages typical of supramolecular ligands is the easy access to these large libraries, and we are currently preparing various libraries to widen the scope of asymmetric reactions.

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